



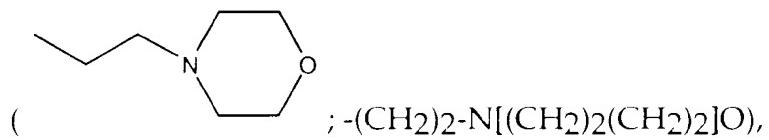
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aminosine, 2-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza-8-aza derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-ethyluracil; 5-propynyluracil and the like.

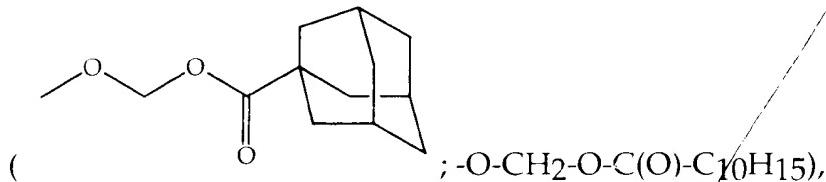
Preferably, B is a 9-purinyl residue selected from guanyl, 3-deazaguanyl, 1-deazaguanyl, 8-azaguanyl, 7-deazaguanyl, adenyl, 3-deazaadenyl, 1-deazaadenyl, 8-azaadenyl, 7-deazaadenyl, 2,6-diaminopurinyl, 2-aminopurinyl, 6-chloro-2-aminopurinyl and 6-thio-2-aminopurinyl, or a B is a 1-pyrimidinyl residue selected from cytosinyl, 5-halocytosinyl, and 5-(C₁-C₃-alkyl)cytosinyl.

The invention compounds, such as those of the formulas (L¹)(RO)P(O)-Z-B, are optionally esterified at the phosphorus atom by the group R defined above. Exemplary R groups include phenyl, 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 2-, 3- and 4-pyridinyl, 2-, 4- and 5-pyrimidinyl, 2-, 3- and 4-alkoxyphenyl (C₁-C₁₂ alkyl including 2-, 3- and 4-methoxyphenyl and 2-, 3- and 4-ethoxyphenyl), 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 2,4-dichlorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C₁-C₁₂ alkyl including 2-, 3- and 4-trifluoromethylphenyl and 2-, 3- and 4-trichloromethylphenyl), 2-, 3- and 4-cyanophenyl, carboalkoxyphenyl (C₁-C₄ alkyl including 2-, 3- and 4-carboethoxyphenyl (-C₆H₄-C(O)-OC₂H₅) and 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dicarboethoxyphenyl), 1-, 2-, 3-, and 4-pyridinyl (-C₅H₄N), 2-, 3- and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms, C₁-C₁₂ alkyl including 4-trifluoromethylbenzyl), alkylsalicylphenyl (C₁-C₄ alkyl including 2-, 3- and 4-ethylsalicylphenyl), 2-, 3- and 4-acetylphenyl, 1,8-dihydroxy-naphthyl (-O-C₁₀H₆-OH or -O-C₁₀H₆-O-), 2,2'-dihydroxybiphenyl (-O-C₆H₄-C₆H₄-O-; both oxygen atoms are linked to the phosphorus atom), alkoxy ethyl [C₁-C₆ alkyl including -CH₂-CH₂-O-CH₃ (methoxy ethyl) and phenoxyethyl], aryloxy ethyl

[C₆-C₉ aryl (including phenoxy ethyl) or C₆-C₉ aryl substituted by OH, NH₂, halo, C₁-C₄ alkyl or C₁-C₄ alkyl substituted by OH or by 1 to 3 halo atoms], -C₆H₄-CH₂-N(CH₃)₂, N-ethylmorpholino



adamantoyl oxymethyl, pivaloyloxy(methoxyethyl)methyl
(-CH(CH₂CH₂OCH₃)-O-C(O)-C(CH₃)₃),



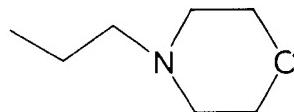
pivaloyloxymethyl (-CH₂-O-C(O)-C(CH₃)₃), pivaloyloxy(methoxymethyl)-methyl (-CH(CH₂OCH₃)-O-C(O)-C(CH₃)₃), pivaloyloxyisobutyl (-CH(CH(CH₃)₂)-O-C(O)-C(CH₃)₃) isobutyryloxymethyl (-CH₂-O-C(O)-CH₂-CH(CH₃)₂), cyclohexanoyl oxymethyl (-CH₂-O-C(O)-C₆H₁₁), phenyl (-C₆H₅), benzyl (-CH₂-C₆H₅), isopropyl (-CH(CH₃)₂), t-butyl (-C(CH₃)₃), -CH₂-CH₃, -(CH₂)₂-C₁₃, -(CH₂)₃-CH₃, -(CH₂)₄-CH₃, -(CH₂)₅-CH₃, -CH₂-CH₂F, -CH₂-CH₂Cl, -CH₂-CF₃, -CH₂-CCl₃, R⁵, NHR^{6A} or N(R^{6A})₂ wherein R⁵ is CH₂C(O)N(R^{6A})₂, CH₂C(O)OR^{6A}, CH₂OC(O)R^{6A}, CH(R^{6A})OC(O)R^{6A}, CH₂C(R^{6A})₂CH₂OH, or CH₂OR^{6A}, NH-CH₂-C(O)O-CH₂CH₃, N(CH₃)-CH₂-C(O)O-CH₂CH₃, NHR⁴⁰, CH₂-O-C(O)-C₆H₅, CH₂-O-C(O)-C₁₀H₁₅, -CH₂-O-C(O)-CH₂CH₃, CH₂-O-C(O)-CH(CH₃)₂, CH₂-O-C(O)-C(CH₃)₃, CH₂-O-C(O)-CH₂-C₆H₅, wherein R^{6A} is C₁-C₂₀ alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N and halogen (1 to 5 halogen atoms), C₆-C₂₀ aryl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N and halogen (1 to 5 halogen atoms) or C₇-C₂₀ aryl-alkyl which is unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N and halogen (1 to 5 halogen atoms), provided that for compounds of formulas N(R^{6A})₂, CH₂C(O)N(R^{6A})₂, CH₂C(O)OR^{6A}, CH₂OC(O)R^{6A}, CH(R^{6A})OC(O)R^{6A} and CH₂C(R^{6A})₂CH₂OH, the total number of carbon atoms present is less than 25 (preferably the number of carbon atoms present is about 4 to about 14) and R⁴⁰ is C₁-C₂₀ alkyl.

Exemplary R groups include X¹, X², X³, R⁵, NHR^{6A} and N(R^{6A}), wherein

X¹ is selected from the group consisting of 2- and 3-pyrrolyl, 2- and 3-thienyl, 2- and 4-imidazolyl, 2-, 4- and 5-oxazolyl, 3- and 4-isoxazolyl, 2-, 4- and 5-thiazolyl, 3-, 4- and 5-isothiazolyl, 3- and 4-pyrazolyl, 1-, 2-, 3- and 4-pyridinyl and 2-, 4- and 5-pyrimidinyl;

X² is selected from the group consisting of phenyl, benzyl, -C₆H₄CH₂-N(CH₃)₂, 2-, 3- and 4-alkoxyphenyl (C₁-C₁₂ alkyl including 2-, 3- and 4-methoxyphenyl and 2-, 3- and 4-ethoxyphenyl), 2-, 3- and 4-halophenyl (including 2-, 3- and 4-fluorophenyl), 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dihalophenyl (including 2,4-difluorophenyl and 2,4-dichlorophenyl), 2-, 3- and 4-haloalkylphenyl (1 to 5 halogen atoms, C₁-C₁₂ alkyl including 2-, 3- and 4-trifluoromethylphenyl and 2-, 3-, and 4-trichloromethylphenyl), 2-, 3- and 4-cyanophenyl, carboalkoxyphenyl (C₁-C₄ alkyl including 2-, 3- and 4-carboethoxyphenyl (-C₆H₄-C(O)-OC₂H₅) and 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dicarboethoxyphenyl), 2-, 3-, and 4-nitrophenyl, 2-, 3- and 4-haloalkylbenzyl (1 to 5 halogen atoms (C₁-C₁₂ alkyl including 4-trifluoromethylbenzyl), alkylsalicylphenyl (C₁-C₄ alkyl including 2-, 3- and 4-ethylsalicylphenyl), 2-, 3- and 4-acetylphenyl, phenyl substituted by methoxy, ethoxy, OH, NH₂, halo, C₁-C₄ alkyl or C₁-C₄ alkyl substituted by OH or by 1 to 3 halo atoms, and -C₁₀H₆OH; and

X³ is selected from the group consisting of alkoxy ethyl (C₁-C₆ alkyl including -CH₂-CH₂-O-CH₃).



adamantoyloxymethyl, pivaloyloxy(methoxyethyl)methyl

(-CH(CH₂CH₂OCH₃)-O-C(O)-C(CH₃)₃), 1-adamantane-
carbonyloxymethyleneoxymethyl-, pivaloyloxymethyl (-CH₂-O-C(O)-C(CH₃)₃),
pivaloyloxy(methoxymethyl)-methyl (-CH(CH₂OCH₃)-O-C(O)-C(CH₃)₃,
pivaloyloxyisobutyl (-CH(CH(CH₃)₂)-O-C(O)-C(CH₃)₃), isobutyryloxymethyl
(-CH₂-O-C(O)-CH₂-CH(CH₃)₂), cyclohexanoyloxymethyl
(-CH₂-O-C(O)-C₆H₁₁), isopropyl (-CH(CH₃)₂), t-butyl (-C(CH₃)₃),
-CH₂-CH₃, -(CH₂)₂-CH₃, -(CH₂)₃-CH₃, -(CH₂)₄-CH₃, -(CH₂)₅-CH₃, -CH₂-
CH₂F, -CH₂CH₂Cl, -CH₂-CF₃ and -CH₂-CCl₃;

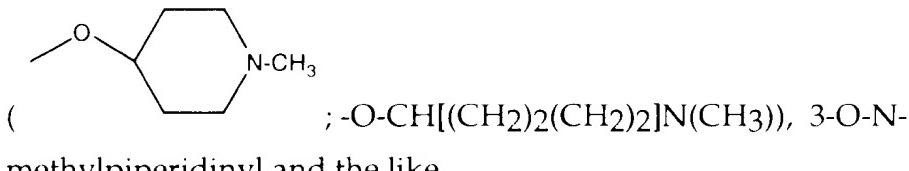
or two R groups are joined to form substituents selected from the group
consisting of -C₁₀H₆- and -C₆H₄C₆H₄-,

wherein R⁵ is selected from the group consisting of CH₂C(O)N(R^{6A})₂,
CH₂C(O)OR^{6A}, CH₂OC(O)R^{6A}, CH(R^{6A})OC(O)R^{6A}, CH₂C(R^{6A})₂CH₂OH,
CH₂OR^{6A}, NH-CH₂-C(O)O-CH₂CH₃, N(CH₃)-CH₂-C(O)O-CH₂CH₃, NHR⁴⁰,
CH₂-O-C(O)-C₆H₅, CH₂-O-C(O)-C₁₀H₁₅, -CH₂-O-C(O)-CH₂CH₃,
CH₂-O-C(O)-CH(CH₃)₂, CH₂-O-C(O)-C(CH₃)₃, and CH₂-O-C(O)-CH₂-C₆H₅;

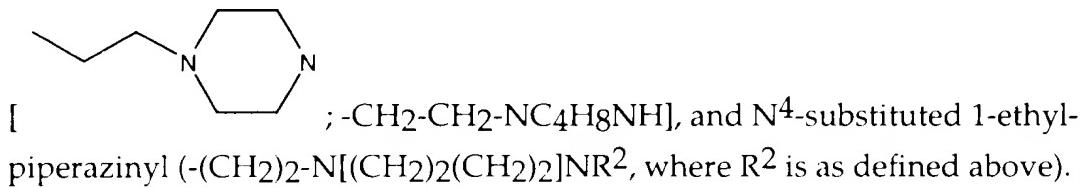
wherein R^{6A} is selected from the group consisting of C₁-C₂₀ alkyl which
is unsubstituted or substituted by substituents independently selected from the
group consisting of OH, O, N and halogen (1 to 5 halogen atoms), C₆-C₂₀ aryl
which is unsubstituted or substituted by substituents independently selected
from the group consisting of OH, O, N and halogen (1 to 5 halogen atoms) or C₇-
C₂₀ aryl-alkyl which is unsubstituted or substituted by substituents
independently selected from the group consisting of OH, O, N and halogen (1 to
5 halogen atoms), wherein O and N are substituted for carbon and provided that
the total number of R⁵ or R carbon atoms is less than 25 (preferably about 4 -
about 14) for compounds where R⁵ or R is selected from the group consisting of
N(R^{6A})₂, CH₂C(O)N(R^{6A})₂, CH₂C(O)OR^{6A}, CH₂OC(O)R^{6A},
CH(R^{6A})OC(O)R^{6A} and CH₂C(R^{6A})₂CH₂OH; and

wherein R⁴⁰ is C₁-C₂₀ alkyl.

The invention compounds are optionally alkylated at the α -nitrogen atom of the amino acid by the R¹ group defined above. Exemplary R¹ groups include H, CH₃, CH₂CH₃, benzyl, 4-O-N-methylpiperidinyl



The invention compounds are optionally esterified at the amino acid carboxyl moiety by the R⁴ group defined above. Exemplary R⁴ groups include H, methyl, ethyl, propyl, isopropyl, butyl, t-butyl (C(CH₃)₃), phenyl (-C₆H₅), benzyl (-CH₂-C₆H₅), 1-pyridyl, 3-pyridyl, 1-pyrimidinyl, N-ethylmorpholino (-CH₂-CH₂-N[(CH₂)₂(CH₂)₂]O), N-2-propylmorpholino (-CH(CH₃)-CH₂-N[(CH₂)₂(CH₂)₂]O), methoxyethyl (-CH₂-CH₂-O-CH₃), 4-N-methylpiperidyl (-CH[(CH₂)₂(CH₂)₂]N(CH₃)), 3-N-methylpiperidyl, phenol which is 2-, 3-, or 4-substituted by N(R³⁰)₂ where R³⁰ is independently H or C₁-C₆ alkyl unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, COOR⁴ and halogen or C₆-C₁₂ aryl unsubstituted or substituted by substituents independently selected from the group consisting of OH, O, N, COOR⁴, N(R⁷)₂ and halogen (including 2-, 3-, and 4-N,N-dimethylaminophenol and 2-, 3-, and 4-N,N-diethylaminophenol), 1-ethylpiperazinyl



Additional compounds that are included in the invention are nucleotide analog dimers that are linked via an amino or carboxyl group. As used herein, dimers (or trimers) refer to the presence of two (or three) nucleoside residues that comprise a compound. Thus, a -L¹-P(O)(L¹)-Z-B or -P(O)(L¹)-Z-B radical covalently linked to a -L¹-P(O)(L¹)-Z-B or -P(O)(L¹)-Z-B radical gives B-Z-P(O)(L¹)-P(O)(L¹)-Z-B, B-Z-P(O)(L¹)-L¹-P(O)(L¹)-Z-B or B-Z-P(O)(L¹)-L¹-P(O)(L¹)-Z-B.